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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,391	10/28/2003	Jeffrey Isner	47624-CIP (71417)	6371

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EXAMINER	
NGUYEN, QUANG	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/696,391	ISNER ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-52,54-65 and 68-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-52, 54-65 and 68-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 9/25/08 was entered for the purpose of a compact prosecution, even though it does not comply with the requirements of 37 CFR 1.121(c) because the status of claim 59 should be "Previously presented" rather "Currently amended" as presented because there is no amendment to the claim.

Claims 49-52, 54-65 and 68-70 are pending in the present application, and they are examined on the merits herein.

Priority

The present application is a continuation-in-part of U.S. Serial No. 09/265,071, filed on 3/9/1999, now issued US 6,676,937, which claims benefit of the provisional application 60/077,262, filed on 3/9/1998.

Upon review of the specifications of the U.S. Serial No. 09/265,071 and the provisional application 60/077,262 and comparison with the specification of the present application, it is determined that the examined claims are only entitled to the priority benefit of the filing date of 10/28/2003 for the following reasons. This is because there is no written support in either the parent U.S. application or in the provisional application for a method of inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment having the specific recited steps (a)-(c), and particularly comprising **the step of monitoring a cardiac function as recited in step (c)**; or **the step of administering to the treated mammal a broad genus of an anti-coagulant**

before, during, or after administration of the nucleic acid to the mammal (limitation of claim 61).

Accordingly, pending claims 49-52, 54-65 and 68-70 are only entitled to the priority date of 10/28/2003 for the reasons set forth above.

Should Applicants overcome the assigned priority date of 10/28/2003, claims 49-52, 54-65 and 68-70 are only entitled at best to the effective filing date of 3/9/1999 because the provisional application 60/077,262, filed on 3/9/1998 does not have a written support for a concept of co-administering a broad genus of an angiogenic factor or an effective fragment thereof to induce new blood vessel growth in the myocardial tissue of the mammal and ***increasing the frequency of EPC in the mammal,*** *particularly VEGF, SCF and any CSF, with an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 49, 52, 54-56, 58-65 and 68-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307; Cited previously) in view of Hammond et

al. (US Patent 5,880,090; IDS) and Dillmann et al. (US 6,605,274; Cited previously) for essentially the same reasons already set forth in the Office action mailed on 2/13/07 (pages 4-8). ***The same rejection is restated below.***

The instant claims are directed to a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such a treatment comprising: a) administering an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and b) administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, thereby inducing the new blood vessel growth in the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells in the mammal; and c) monitoring a cardiac function by echocardiography, ventricular end-diastolic dimension, end-systolic dimension, fractional shortening, wall motion score index, electromechanical mapping, cardiac angiography or LV systolic pressure, wherein the method improves said cardiac function.

Isner teaches a method for enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having cerebrovascular ischemia, renal ischemia, pulmonary ischemia, limb ischemia, ischemic cardiomyopathy and **myocardial ischemia** (page 4, lines 5-23). The method comprises the step of injecting to said tissue with an effective amount of a nucleic acid capable of expressing an angiogenic protein by any injection means, and the nucleic acid may be carried by vehicles such as cationic liposomes, adenoviral vectors and that **nucleic acid encoding different**

angiogenic proteins may be used separately or simultaneously (page 4, line 25 continues to line 8 of page 5). **Angiogenic proteins include aFGF, bFGF, VEGF (including VEGF165, see page 15, line 19), EGF, PDGF, PD-ECGF, HGF, colony stimulating factor (CSF), macrophage-CSF (M-CSF), granulocyte/macrophage CSF (GM-CSF) and nitric oxide synthase or muteins or portions thereof** (page 5, lines 10-22). Isner also teaches that the nucleic acid encoding an angiogenic protein is inserted into a cassette where it is operably linked to a promoter that is capable of driving expression of the protein in cells of the desired target tissue (page 9, line 28 continues to line 20 of page 10). **Isner further teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, while simultaneously inducing angiogenesis, including, for example, nitric oxide synthase, L-arginine, fibronectin, urokinase, plasminogen activator and heparin** (page 11, lines 15-19). Isner also discloses that catheters have been used for gene delivered in the art (page 1, line 23 continues to line 30 of page 2).

Isner does not teach specifically a further administration of an effective amount of at least one angiogenic factor, specifically a stem cell factor (SCF), a colony stimulating factor (CSF), or an effective fragment thereof into the mammal to induce new blood vessel growth **and to increase the frequency of endothelial progenitor cells**, even though Isner teaches that nucleic acids encoding different angiogenic proteins such as aFGF, bFGF, VEGF (including VEGF165, see page 15, line 19), EGF, PDGF, PD-ECGF, HGF, colony stimulating factor (CSF), macrophage-CSF (M-CSF),

granulocyte/macrophage CSF (GM-CSF) and nitric oxide synthase or muteins or portions thereof may be used separately or simultaneously; and that an angiogenic factor can be combined **with other genes or their encoded gene products to enhance the activity of targeted cells**. Isner also does not teach specifically to monitor a cardiac function by one of the recited approaches, even though Isner discloses monitoring collateral artery development in the medial thigh by angiography (page 21, lines10-25) or measuring calf blood pressure for physiologic assessment (page 22, liens 12-27).

At the filing date of the present application (10/28/03) Hammond et al already taught that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient (see at least Summary of the invention). Hammond et al further note that CD34+ circulating cells in the blood can participate in the repair of ischemic tissue (col. 3, lines 28-37).

Dillmann et al already taught that clinical signs of improvement in cardiac performance and accommodation of stresses associated with congestive heart failure (CHF) are well known to those of ordinary skill in the cardiological art and may be determined, for example, by monitoring blood flow, cardiac pumping volume and ventricular pressure by for example, angiography and echocardiography, calcium transport rates, tolerance studies (col. 14, lines 14-26), as well as measurements of left

ventricular end-diastole dimension (LVEDD), LV end-systolic dimension (LVESD), and fractional shortening (col. 25, line 37 continues to line 5 of col. 26).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Isner by further administering specifically to the treated mammal an effective amount of at least one of SCF or CSF or an effective fragment thereof to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells in the treated mammal in light of the teachings of Hammond et al. Additionally, it would also have been obvious for an ordinary skilled artisan to monitor the cardiac function in the mammal treated for myocardial ischemia using any of the means recited in claim either 49 or claim 69 in light of the teachings of Dillmann et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because Hammond et al. already demonstrated that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient; and this mobilization of endothelial cell progenitors would further enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the desired therapeutic outcome. Additionally, any of the means to monitor cardiac function taught by Dillmann et al is well-known and conventionally used by those of ordinary skill in the cardiological art to monitor clinical signs of improvement in cardiac performance, particularly for the treatment of ischemic cardiomyopathy and/or

myocardial ischemia in this instance. It is further noted that the monitoring means is not the patentable subject matter for the claimed methods because Applicants specifically state "cardiac function is monitored in the mammal by one or more combination of standard approaches to evaluate therapeutic outcome" (page 12, lines 24-25). The modified method resulting from the combined teachings of Isner, Hammond et al., and Dillman et al. is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner, Hammond et al., and Dillman et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 50-51 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307; Cited previously) in view of Hammond et al. (US Patent 5,880,090; IDS) and Dillmann et al. (US 6,605,274; Cited previously) as applied to claims 49, 52, 54-56, 58-65 and 68-69 above, and further in view of Asahara et al. (EMBO Journal 18:3964-3972, 1999) for essentially the same reasons already set forth in the Office action mailed on 2/13/07 (pages 8-10). ***The same rejection is restated below.***

The combined teachings of Isner, Hammond et al. and Dillmann et al. were presented above. However, none of the references teaches specifically a further administration to the mammal an effective amount of a VEGF or an effective fragment

thereof to induce the new blood vessel growth in the myocardial tissue of the mammal and increasing the frequency of endothelial progenitor cells in the mammal.

However at the filing date of the present application (10/28/2003), Asahara et al already demonstrated that recombinant human VEGF165 is capable of inducing mobilization of bone marrow-derived EPCs to augment neovascularization *in vivo* to complement its direct effect on fully differentiated endothelial cells (see at least the abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan to further modify the method of Isner, Hammond et al and Dillman et al. by also further administering to the treated mammal an effective amount of at least VEGF or an effective fragment thereof such as VEGF165 to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells in the treated mammal in light of the teachings of Asahara et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because Asahara et al already demonstrated that recombinant human VEGF165 is capable of inducing mobilization of bone marrow-derived EPCs to augment neovascularization *in vivo* to complement its direct effect on fully differentiated endothelial cells; and this mobilization of endothelial cell progenitors would further enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the desired therapeutic outcome. The modified method resulting from the combined teachings of Isner,

Hammond et al., Dillman et al., and Asahara et al. is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner, Hammond et al., Dillman et al., and Asahara et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 70 is rejected under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307; Cited previously) in view of Hammond et al. (US Patent 5,880,090; IDS) and Dillmann et al. (US 6,605,274; Cited previously) as applied to claims 49, 52, 54-56, 58-65 and 68-69 above, and further in view of either Coleman (US 7,273,751) or Hu et al. (US 6,734,285) for essentially the same reasons already set forth in the Office action mailed on 3/25/08 (pages 10-12). ***The same rejection is restated below.***

The combined teachings of Isner, Hammond et al. and Dillmann et al were already presented above. However, none of the references teaches specifically the use of an effective amount of a nucleic acid encoding VEGF-2 for inducing new blood vessel growth in myocardial tissue of a mammal in need, even thought Isner already taught a method for enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having cerebrovascular ischemia, renal ischemia, pulmonary ischemia, limb

ischemia, ischemic cardiomyopathy and myocardial ischemia using an effective amount of a nucleic acid encoding a VEGF.

However at the filing date of the present application, both Coleman and Hu et al already taught separately that VEGF-2 is a potent angiogenic factor, and VEGF-2 polypeptide as well a nucleic acid molecule encoding VEGF-2 polypeptide are useful at least for treating various cardiovascular disorders, including myocardial ischemia, congestive heart failure, congestive cardiomyopathy among others (see at least col. 45, line 13 continues to line 63 of col. 56 in US 7,273,751; col. 45, line 1 continues to line 31 of col. 56 in US 6,734,285).

Accordingly, it would have been obvious for an ordinary skilled artisan to further modify the method of Isner, Hammond et al and Dillman et al. by also administering to the treated mammal an effective amount of a nucleic acid encoding VEGF-2 into the myocardial tissue in light of the teachings of either Coleman or Hu et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because both Coleman and Hu et al already taught separately that VEGF-2 is a potent angiogenic factor, and VEGF-2 polypeptide as well a nucleic acid molecule encoding VEGF-2 polypeptide are useful at least for treating various cardiovascular disorders, including myocardial ischemia, congestive heart failure, congestive cardiomyopathy among others. The modified method resulting from the combined teachings of Isner, Hammond et al., Dillman et al., and either Coleman or Hu et al. is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Isner, Hammond et al., Dillman et al., and either Coleman or Hu et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect the above rejections in the Amendment filed on 9/25/08 (pages 6-12) have been fully considered but they are respectfully not found persuasive. The examiner notes that Applicants presented the same lines of arguments as those already presented in the previous amendment dated 3/04/08; coupled with new arguments regarding to newly cited Coleman and Hu references for the new ground of rejection for claim 70. Applicant's arguments and the Examiner's responses are summarized below.

1. With respect to the rejection under 35 U.S.C. 103(a) as being unpatentable over Isner in view of Hammond et al. and Dillmann et al., once again Applicants argue that the Examiner must show some particular teaching or suggestion within the references themselves that the combination should be made. Applicants further argue that Hammond et al only proposed that the circulating CD34+or Flk-1+ cells participating in the repair of ischemic tissue, but the reference fails to teach or suggest employing an effective amount of a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue;

administering to the mammal an effective amount of at least one angiogenic factor or an effective amount thereof, thereby inducing the new blood vessel growth in the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells (EPC) in the mammal; and monitoring the cardiac function. With respect to the rejection under 35 U.S.C. 103(a) as being unpatentable over Isner in view of Hammond et al. and Dillmann et al. as applied to claims 49, 52, 54-56, 58-65 and 68-69 above, and further in view of Asahara et al., Applicants argue that although Asahara describes the use of VEGF to induce the mobilization of bone marrow-derived EPCs, he failed to appreciate the combination of a nucleic acid encoding at least one angiogenic protein and at least one angiogenic factor, enhances the induction of blood vessel growth in a myocardial tissue. Applicants further argue that Asahara plainly teaches that VEGF is sufficient to induce vasculogenesis, and therefore he teaches away from Applicant's claimed invention. With respect to the rejection under 35 U.S.C. 103(a) as being unpatentable over Isner (WO 97/14307; Cited previously) in view of Hammond et al. (US Patent 5,880,090; IDS) and Dillmann et al. (US 6,605,274; Cited previously) as applied to claims 49, 52, 54-56, 58-65 and 68-69 above, and further in view of either Coleman (US 7,273,751) or Hu et al. (US 6,734,285); Applicants argue basically that both Hu and Coleman fail to provide the necessary motivation to use VEGF-2 in combination with a nucleic acid encoding an angiogenic protein and that both teach that VEGF-2 is efficacious on its own and there is no teaching or suggestion that in either of these references that it is necessary or desirable to administer VEGF-2 in combination with another factor. Applicants further argue that the examiner relies on no less than

five references in making the obviousness rejection, and such reliance belies the alleged obviousness of the claimed invention.

Firstly, it appears that Applicants ignored completely the overall teachings of all of the cited references for each of the above 103(a) rejections, and only considered the teachings of each cited reference in total isolation one from the others. It should also be noted that none of the cited references has to teach every limitation of the claims in a rejection under 35 USC 103(a).

Secondly, it should be noted that Isner teaches clearly that **an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells in a method for enhancing blood vessel formation or an angiogenesis in an ischemic tissue, including ischemic cardiomyopathy or myocardial ischemia, in a mammal (a clear suggestion).** Hammond et al. also taught clearly that **SCF, GM-CSF, G-CSF are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for enhancing the endothelialization of synthetic vascular grafts in a patient. Hammond also notes that CD34+ circulating cells in blood can participate in the repair of ischemic tissue** (col. 3, lines 28-37). Asahara et al further demonstrated that **recombinant human VEGF165 is capable of inducing mobilization of bone marrow-derived EPCs to augment neovascularization *in vivo* to complement its direct effect on fully differentiated endothelial cells**. As already pointed out in the above rejection, it would have been obvious for an ordinary skilled artisan to further modify the method of Isner, Hammond et al and Dillman et al. by also further

administering to the treated mammal an effective amount of at least VEGF or an effective fragment thereof such as VEGF165 to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells in the treated mammal. An ordinary skilled artisan would have been motivated to carry out the above modifications because Asahara et al already demonstrated that recombinant human VEGF165 is capable of inducing mobilization of bone marrow-derived EPCs to augment neovascularization *in vivo* to complement its direct effect on fully differentiated endothelial cells; and this mobilization of endothelial cell progenitors would further enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the desired therapeutic outcome. Additionally, at the filing date of the present application, both Coleman and Hu et al already taught separately that **VEGF-2 is a potent angiogenic factor**, and VEGF-2 polypeptide as well **a nucleic acid molecule encoding VEGF-2 polypeptide are useful at least for treating various cardiovascular disorders, including myocardial ischemia, congestive heart failure, congestive cardiomyopathy among others.** Accordingly, the modified methods resulting from the combined teachings of Isner, Hammond et al., Dillman et al., Asahara et al., Hu et al. and Coleman are indistinguishable from the presently claimed methods. Furthermore, it should be noted that any of the means to monitor cardiac function taught by Dillmann et al is well-known and conventionally used by those of ordinary skill in the cardiological art to monitor clinical signs of improvement in cardiac performance, particularly for the treatment of ischemic cardiomyopathy and/or myocardial ischemia in this instance.

Thirdly, there is no teaching away whatsoever by the Asahara et al, Coleman and Hu et al references. This is because nowhere in anyone of these references that teaches or suggests explicitly that additional angiogenic factor, including a nucleic acid encoding at least one angiogenic protein or an effective fragment therefore, should not be used in combination with the recombinant human VEGF165 or VEGF-2.

Fourthly, there is nothing that is unpredictable about the induction of new blood vessel growth in an ischemic myocardial tissue in a mammal in need thereof in light of the totality of the teachings of at least Isner, Hammond et al, Asahara et al, Coleman and Hu et al as discussed above.

Fifthly, with respect to the number of cited references it should be noted that the number of specific limitation in the claims dictates the number of references to be cited, and not because of the obviousness of the claimed invention.

2. With respect to claims 69-70, Applicants argue that the combination of VEGF expression and GM-CSF and/or SCF administration is unexpectedly effective (a synergistic effect) in inducing new blood vessel growth and improving cardiac function in myocardial tissue *in vivo* as shown in Example 9-12 and pages 45-59. Applicants also argue that Applicants show a synergistic effect of G-CSF and SCF when administered in combination with VEGF-2 gene transfer in both acute myocardial infarction and chronic myocardial ischemia, and none of the cited references teaches or suggests that the combination of VEGF expression and GM-CSF and/or SCF therapy

would have a synergistic effect on new blood vessel growth and would improve cardiac function.

Firstly, please note that there is no surprising or unexpected results obtained by the combo group as argued by Applicants because the obtained results are actually expected. This is because the angiogenic effects contributed by the administration of an effective amount of a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof **are complemented or enhanced** by the effects contributed by the administration of an effective amount of at least one angiogenic factor such as GM-CSF, G-CSF, SCF and VEGF or an effective fragment thereof due to their ability to mobilize bone-marrow derived endothelial progenitors that can participate in the repair of ischemic tissues based on the teachings of Hammond et al. and/or Asahara et al. as discussed above. Moreover, please also note that **GM-CSF, G-CSF and VEGF (particularly VEGF-2 being known as a potent angiogenic factor) are also angiogenic proteins in addition to their ability to mobilize bone-marrow derived endothelial progenitor cells**.

Secondly, it is further noted that the alleged "unexpected results" were obtained in the instant specification for **the specific combination of VEGF-2 gene therapy together with G-CSF and SCF**; but the breadth of claims 69-70 does not limit to this specific combination.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 49, 52, 54-56, 58-65 and 68-69 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 49-61, 63-66, 68-70 and 72 of copending Application No. 10/714,574 in view of Dillmann et al. (US 6,605,274; Cited previously) for essentially the same reasons already set forth in the Office action mailed on 3/25/08 (pages 17-19). ***The same rejection is restated below.***

The instant claims are directed to a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such a treatment comprising: a) administering an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and b) administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, thereby inducing the new blood vessel growth in

the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells in the mammal; and c) monitoring a cardiac function by echocardiography, ventricular end-diastolic dimension, end-systolic dimension, fractional shortening, wall motion score index, electromechanical mapping with a NOGA system, cardiac angiography or LV systolic pressure, wherein the method improves said cardiac function.

Claims 49-61, 63-66, 68-70 and 72 of copending Application No. 10/714,574 are drawn to a method for treating ischemic myocardial tissue of a mammal in need of such a treatment comprising: a) identifying a mammal which has, is suspected of having, or will have the ischemic tissue; b) injecting an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and c) administering to the mammal an effective amount of a colony stimulating factor, including GM-CSF, or an effective fragment thereof, or an effective amount of a cytokine (e.g., GM-CSF and SCF) thereby treating ischemic myocardial tissue of the mammal.

The claims of the present application differ from the claims of the copending Application No. 10/714,574 in reciting the additional step of monitoring a cardiac function by any one of the approaches recited in the Markush group of anyone of claims 49, 69 and 70.

At the filing date of the present application, Dillmann et al already taught that clinical signs of improvement in cardiac performance and accommodation of stresses associated with congestive heart failure (CHF) are well known to those of ordinary skill

in the cardiological art and may be determined, for example, by monitoring blood flow, cardiac pumping volume and ventricular pressure by for example, angiography and echocardiography, calcium transport rates, tolerance studies (col. 14, lines 14-26), as well as measurements of left ventricular end-diastole dimension (LVEDD), LV end-systolic dimension (LVESD), and fractional shortening (col. 25, line 37 continues to line 5 of col. 26).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time the invention was made to modify the method of the copending Application No. 10/714,574 by further monitor the cardiac function in the mammal treated for myocardial ischemia using any of the means recited in anyone of claims 49, 69 and 70 in light of the teachings of Dillmann et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because any of the means to monitor cardiac function taught by Dillmann et al is well-known and conventionally used by those of ordinary skill in the cardiological art to monitor clinical signs of improvement in cardiac performance, particularly for the treatment of ischemic cardiomyopathy and/or myocardial ischemia in this instance.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of the copending Application No. 10/714,574 and Dillmann et al., coupled with a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 49-51 and 57 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 69 of copending Application No. 10/714,574 in view of Dillmann et al. (US 6,605,274; Cited previously) and Asahara et al. (EMBO Journal 18:3964-3972, 1999) for essentially the same reasons already set forth in the Office action mailed on 2/13/07 (pages 17-20). ***The same rejection is restated below.***

The instant claims are directed to a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such a treatment comprising: a) administering an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and b) administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, thereby inducing the new blood vessel growth in the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells in the mammal; and c) monitoring a cardiac function by echocardiography, ventricular end-diastolic dimension, end-systolic dimension, fractional shortening, wall motion score index, electromechanical mapping with a NOGA system, cardiac angiography or LV systolic pressure, wherein the method improves said cardiac function, and wherein the angiogenic factor is a VEGF or an effective fragment thereof.

Claim 69 of copending Application No. 10/714,574 is drawn to a method for treating ischemic myocardial tissue of a mammal in need of such a treatment comprising: a) administering to a mammal an effective amount of a cytokine that mobilizes endothelial progenitor cells; and b) subsequently administering an effective amount of a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue, wherein the method increases the neovascularization of said tissue thereby treating ischemic myocardial tissue of the mammal.

The claims of the present application differ from the claims of the copending Application No. 10/714,574 in reciting the additional step of monitoring a cardiac function by any one of the approaches recited in the Markush group of claim 49, and the angiogenic factor is VEGF or an effective fragment thereof.

At the filing date of the present application, Asahara et al already demonstrated that recombinant human VEGF165 is capable of inducing mobilization of bone marrow-derived EPCs to augment neovascularization *in vivo* to complement its direct effect on fully differentiated endothelial cells (see at least the abstract).

Additionally, Dillmann et al already taught that clinical signs of improvement in cardiac performance and accommodation of stresses associated with congestive heart failure (CHF) are well known to those of ordinary skill in the cardiological art and may be determined, for example, by monitoring blood flow, cardiac pumping volume and ventricular pressure by for example, angiography and echocardiography, calcium transport rates, tolerance studies (col. 14, lines 14-26), as well as measurements of left

ventricular end-diastole dimension (LVEDD), LV end-systolic dimension (LVESD), and fractional shortening (col. 25, line 37 continues to line 5 of col. 26).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time the invention was made to modify the method of the copending Application No. 10/714,574 by further monitor the cardiac function in the mammal treated for myocardial ischemia using any of the means recited in claim 67 in light of the teachings of Dillmann et al., as well as further administering to the treated mammal an effective amount of at least VEGF or an effective fragment thereof such as VEGF165 to induce new blood vessel growth and to increase the frequency of endothelial progenitor cells in the treated mammal in light of the teachings of Asahara et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because any of the means to monitor cardiac function taught by Dillmann et al is well-known and conventionally used by those of ordinary skill in the cardiological art to monitor clinical signs of improvement in cardiac performance, particularly for the treatment of ischemic cardiomyopathy and/or myocardial ischemia in this instance. Furthermore, Asahara et al already demonstrated that recombinant human VEGF165 is capable of inducing mobilization of bone marrow-derived EPCs to augment neovascularization *in vivo* to complement its direct effect on fully differentiated endothelial cells; and this mobilization of endothelial cell progenitors would further enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the desired therapeutic outcome.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of the copending Application No. 10/714,574, Dillmann et al., and Asahara et al., coupled with a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

This is a provisional obviousness-type double patenting rejection.

It is noted that the above provisional obviousness-type double patent rejections are not the only rejections in the instant application.

Conclusions

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/QUANG NGUYEN/
Primary Examiner, Art Unit 1633